

Claims of an association between drinking water, contaminated by several recognised carcinogens, and childhood leukaemia have been dismissed after careful re-evaluation,²⁵ and such a relation could not be shown in other instances.²⁶ The hypothesis that nitrates in water and vegetables cause cancer of the stomach has been neither confirmed nor refuted.²⁴ Unfortunately, much of the evidence stemmed from animal experiments and was supported mainly by geographical correlations (in which other factors associated with the outcome cannot be controlled for).²⁷ The greatly feared long-term effects of pesticides on mortality in man have likewise not been confirmed,²⁸ although an estimated quarter of a million people die each year from acute pesticide poisoning in developing countries.²⁹

Why has scientific investigation not revealed a mortality excess even where it would have been expected? There are several possible explanations. First, the magnitude of the pollutants' effect on health is probably much lower than extrapolations from experiments suggest, and the exposures do not normally lead to a fatal outcome. Second, the doses received by general populations are so low that even established carcinogens cause very few cases. Thus it has been estimated that, in the US, non-occupational exposure to asbestos causes 2 mesotheliomas and 5 lung cancers per million population a year.³⁰ With its long latency, this effect clearly will not be detected by existing methods. Third, some widely used substances such as furans or lead have become so common in our environment that it is virtually impossible to identify a totally unexposed population with whom an exposed group could be compared.³ Last, studies are often difficult to conduct because of small numbers of cases, inaccurate measurement of exposure and confounding variables, and misleading classification of outcome.

From published evidence, environmental pollution is unlikely to result in gross excess mortality, and therefore cannot be responsible for variations in death rates between populations. What can be said of non-carcinogenic effects? The evidence is even less secure than for cancer. Coming back to eastern European experience, factors other than air pollution are likely to be responsible for poor health. The lack of evidence of a gross effect on mortality does not exonerate pollution from fatal consequences at very high exposures or from damaging effects on other aspects of health. A small effect on a large number of people may have enormous public health importance. Effects should be sought at more subtle levels of health damage—for example, reproductive and developmental outcomes and morbidity.

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New treatment for tyrosinaemia

In this issue (p 813) Lindstedt and colleagues report a radically new approach to the treatment of a serious, life-threatening condition. They describe the use of an inhibitor of the enzyme 4-hydroxyphenylpyruvate dioxygenase in hereditary tyrosinaemia type 1. This compound is 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC).

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Hereditary tyrosinaemia is a metabolic disorder characterised by cirrhosis and hypophosphataemic rickets. Clinical severity is variable. Death can occur in the first year of life from liver failure or, in the more chronic form, in the first two decades, often from hepatoma. Acute porphyric crises are an important cause of morbidity and mortality.^{1,2} The enzyme defect in tyrosinaemia type 1 was defined by the group that included Lindstedt in 1977.³ They correctly suggested that the primary defect was a deficiency of fumarylacetoacetate hydratase (EC 3.7.1.2.), which catalyses the last step of tyrosine degradation. Treatment with a diet restricted in phenylalanine and tyrosine helps the renal disease but does not prevent progressive liver failure or the development of hepatoma. Until now liver transplantation was the only successful treatment available. The timing of such a procedure is crucial. In the most acute form it is often not possible to do a transplant in time, partly because of the clinical severity and partly because of the limited availability of donor organs of the correct size. In the more chronic forms there is the desire to keep the child going as long as possible and yet carry out the life-saving procedure before hepatoma has developed. Donor organ shortage is again a problem, as is the morbidity and mortality associated with the procedure. However, until Lindstedt's work there seemed to be no alternative to this approach.

Five patients with type 1 tyrosinaemia, including one with the acute neonatal form, have been studied for between 7 and 9 months. NTBC inhibits an enzyme at a stage preceding the fumarylacetoacetate hydratase deficiency and thus prevents the formation of compounds thought to be responsible for the liver and kidney injury and of succinylacetone which inhibits porphobilinogen synthetase. The researchers speculate that this agent prevents the progressive liver damage and the acute porphyric crises. Although follow-up is short, the response in these patients is encouraging. There was an improvement in wellbeing and in standard liver function tests in all cases. There was also a fall in α -fetoprotein concentration in all patients, although in the eldest the value rose again and that patient subsequently received a transplant. In three patients computed tomographic appearances of the liver improved. It was not possible directly to estimate the degree of inhibition of 4-hydroxyphenylpyruvate dioxygenase. However, by indirect measurements it seems that the enzyme was totally or almost totally inhibited. Excretion of succinylacetone fell and activity of porphobilinogen synthetase increased.

Both the quality of life and life expectancy in type 1 tyrosinaemia could be greatly improved if these results are confirmed. Early treatment is most likely to be successful.

Volunteering for research

Subjects for medical research are almost always selected from a larger pool of potential candidates and various procedures are adopted to ensure that the final sample is representative of the relevant population. An investigation can be worthless if subject selection is confounded with another factor that is known to affect the dependent variable of interest. The use of human subjects in research invokes two conflicting sets of considerations. First, researchers must consider the benefits that might accrue from their work. Occasionally the knowledge gained will benefit the subjects themselves; the beneficiaries are more likely to be the researcher, the wider scientific community, and the community as a whole, in that order. Against these benefits one has to weigh the rights and needs of the subjects. There are very few circumstances in which they should be exposed to dangerous procedures, and we recognise the right of subjects to be adequately informed about the experimental methods and to decline to participate. If sufficient numbers of subjects decline to take part in a study a bias may be introduced into the sample, especially if the reasons for refusal are confounded with the dependent measures. In extreme circumstances such bias may yield seriously misleading results. Refusal rates vary according to the way in which subjects are approached. Postal surveys, for example, often yield participation rates of less than 50%; the individual approach secures much higher recruitment rates.

The reasons why some subjects refuse to participate in research are therefore of more than passing interest. The matter has not been studied much by empirical researchers, perhaps because it is difficult to persuade individuals to answer further questions once they have declined participation. Harth and co-workers^{1,2} achieved this goal with parents who either did or did not volunteer their children for a randomised, double-blind placebo-controlled trial of a new oral anti-asthma drug (ketotifen). Volunteering and non-volunteering parents were followed up and asked several questions; they also completed a battery of psychological tests about interpersonal values, self-esteem, and personality. Volunteering parents, by comparison with their non-volunteering counterparts, were significantly less well educated and less likely to be in professional and managerial occupations; they also used more habit-forming substances, enjoyed less social support, and displayed greater health-seeking behaviour. With respect to psychological measures, the volunteering parents put more value on benevolence and less on power and prestige, displayed much lower self-esteem, and showed lower confidence and emotional stability.

These findings have important implications for the interpretation of scientific results and for the ethical conduct of scientific investigations. In particular, they give credence to the hypothesis that people who agree

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